

Comparison between prostaglandin E₁ and epoprostenol (prostacyclin) in infants after heart surgery

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Abstract

Objective—To study the dose response characteristics of prostaglandin E₁ and epoprostenol (prostacyclin) and directly to compare their effectiveness as pulmonary vasodilators in infants with pulmonary hypertension.

Design—A crossover design with each patient receiving both drugs in random order.

Setting—Infants were studied in the intensive care unit while they were sedated, paralysed, and ventilated.

Patients—Twenty infants who had undergone corrective cardiac surgery and who were in sinus rhythm, had stable haemodynamic function, and had a pulmonary artery catheter in place. All infants were receiving dopamine and phenoxybenzamine.

Interventions—Baseline haemodynamic measurements were taken and an infusion of the first drug was started at the lowest dose: after 20 minutes the measurements were repeated and the dose increased. This protocol was repeated for all doses of both drugs: 10, 30, and 100 ng/kg/min of prostaglandin E₁ and 5, 10, and 25 ng/kg/min of epoprostenol. Cardiac output was measured by the pulsed Doppler ultrasound method.

Main outcome measures—Pulmonary and systemic vascular resistances were calculated from the cardiac output and compared by the Wilcoxon signed ranks test.

Results—Both prostaglandin E₁ and epoprostenol were effective vasodilators: 5 ng/kg/min of epoprostenol was equivalent to 30 ng/kg/min of prostaglandin E₁.

Conclusions—Neither drug showed pulmonary specificity.

heart disease who are ductus dependent,⁶ but there are few published reports of its use as a pulmonary vasodilator in infants and children.^{7,8}

Prostacyclin, identified in 1976, is the main arachidonic acid metabolite formed by vascular endothelium.² It is a more potent inhibitor of platelet aggregation than PGE₁ and may also play a part in modulating pulmonary vascular tone, thereby contributing to the thromboresistance of endothelial cells.² Early reports of its use in children suggested that it caused highly selective pulmonary vasodilatation^{9,10}; however, in larger studies PGI₂ was a consistent but non-selective vasodilator.¹¹⁻¹³ As epoprostenol, prostacyclin is used clinically both to assess the reversibility of pulmonary vasoconstriction before surgery^{11,14} and as long term treatment for patients with primary pulmonary hypertension.¹⁵

In infants with cardiac lesions associated with high pulmonary blood flow severe pulmonary vasoconstriction can develop in response to adverse factors after operation.^{16,17} PGE₁ and epoprostenol are both used in the management of reactive pulmonary hypertension but there is no reported comparison of their efficacy in infants. This study was conducted to document the dose response characteristics of PGE₁ and epoprostenol and directly to compare their effectiveness as pulmonary vasodilators.

Patients and methods

PATIENTS

The mean age of the 20 patients we studied was 2.8 months (range 3 days–6 months), and their mean weight was 4.2 kg (3.2–6.2 kg). The diagnoses were ventricular septal defect (nine cases), complete atrioventricular canal (five cases), total anomalous pulmonary veins (four cases), transposition of the great vessels (one case), and truncus arteriosus (one case).

METHODS

The study was carried out in the Intensive Care Unit at the Royal Children's Hospital, a multidisciplinary unit that has 600 cardiac surgical admissions a year. Patients undergoing intracardiac repair were eligible for the study if they were less than 12 months old, in sinus rhythm, had no bleeding, showed less than 5% change in cardiovascular variables over the previous hour, and had a pulmonary artery catheter in place. Informed parental consent and the approval of the ethics committee were

Prostaglandin E₁ and epoprostenol (prostacyclin, PGI₂) are endogenous prostaglandins with potent vasodilatory effects and similar structures and properties.¹² PGE₁ was the first prostaglandin to be isolated.¹² It is used as a pulmonary vasodilator in patients with pulmonary hypertension^{3,4} and though the pulmonary circulation can rapidly metabolise PGE₁,⁵ systemic vasodilatation often accompanies doses large enough to cause pulmonary vasodilatation.⁴ It is used extensively to maintain ductal patency in infants with congenital

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Accepted for publication
11 March 1991

obtained. Patients were studied 4–48 hours after operation and were given a morphine infusion (10–30 µg/kg/h), neuromuscular blockade with pancuronium (0.1 mg/kg as required), inotropic treatment (dopamine 5–10 µg/kg/min), and vasodilatation with intravenous phenoxybenzamine (1 mg/kg as a loading dose intraoperatively, then 0.5–1 mg/kg every 8–12 hours). The dopamine infusion rate, arterial pH, and P_{aCO_2} were held constant during the study.

Monitoring included continuous heart rate, mean systemic and pulmonary arterial pressures, and right and left atrial pressures, measured via catheters placed at operation. The cardiac output was measured non-invasively by the pulsed Doppler ultrasound method¹⁸ with a Vingmed SD-100 unit (Vingmed Horten, Horten, Norway). PGE_1 (Prostin VR Pediatric, Upjohn, Kalamazoo, MI 49001, USA) was diluted in 0.9% saline solution; epoprostenol (Flolan, Wellcome, UK) was diluted in glycine buffer and then 0.9% saline according to the manufacturer's instructions. The drugs were infused into a central or peripheral intravenous line by a syringe pump. The doses of PGE_1 used were 10, 30, and 100 ng/kg/min, and the doses of epoprostenol were 5, 10, and 25 ng/kg/min.

We studied 20 patients; each received an infusion of PGE_1 and epoprostenol given in random order. After baseline measurements were taken an infusion of the first drug was started at the lowest dose; after 20 minutes the measurements were repeated and the infusion rate was increased. This sequence was repeated for each dose of the first drug and then for the other drug, allowing a washout period of 20 minutes. Each drug infusion was started at the

lowest dose because of the risk of systemic hypotension. Colloid was given if required to keep left atrial pressure constant.

Derived variables were calculated according to the following formulas: cardiac index ($l/min/m^2$) = cardiac output (l/min)/body surface area (m^2); systemic vascular resistance ($dyn.s.cm^{-5}$) = (mean systemic arterial pressure – right atrial pressure) \times 79.9/cardiac output; pulmonary vascular resistance ($dyn.s.cm^{-5}$) = (pulmonary artery pressure – left atrial pressure) \times 79.9/cardiac output.

We used the Wilcoxon signed ranks test to compare the haemodynamic values at each dose of the drugs with baseline values and to compare the effects of one drug with those of the other.

Results

Table 1 shows the effects of PGE_1 on the haemodynamic indices and table 2 the effects of epoprostenol on the haemodynamic indices.

Both drugs produced a decrease in pulmonary and systemic vascular resistance (figs 1 and 2) and an increase in the cardiac index (fig 3); PGE_1 at 30 and 100 ng/kg/min produced vasodilatation approximately equal to that produced by 5 and 10 ng/kg/min of epoprostenol respectively. Neither drug, however, showed any specificity for the pulmonary circulation. To compare their degree of pulmonary specificity we calculated a quantitative value of the relative effects of PGE_1 and epoprostenol from the absolute differences between the change in the pulmonary and systemic vascular resistances from control values at each dose. These differences for equivalent doses were then compared by the Wilcoxon signed ranks

Table 1 Effects of prostaglandin E_1 (PGE_1) infusion on haemodynamic indices in 20 infants (mean (SD))

Index	Control (n = 20)	Dose of PGE_1		
		10 ng/kg/min (n = 20)	30 ng/kg/min (n = 20)	100 ng/kg/min (n = 20)
HR (beats/min)	156 (18)	161 (20)*	159 (16)	158 (16)
MAP (mm Hg)	54.4 (8.0)	53.9 (9.9)	52.0 (8.1)*	50.8 (9.1)*
PAP (mm Hg)	21.3 (5.1)	21.2 (5.4)	20.4 (4.4)*	19.5 (4.8)*
LAP (mm Hg)	8.0 (2.0)	8.2 (2.1)	7.9 (1.9)	7.8 (1.9)
RAP (mm Hg)	6.2 (2.0)	6.4 (2.2)	6.3 (2.0)	6.3 (2.4)
CI ($l/min/m^2$)	4.2 (1.3)	4.3 (1.3)	4.4 (1.4)*	4.5 (1.4)*
SVR ($dyn.s.cm^{-5}$)	3793 (1153)	3622 (1017)	3427 (1029)*	3312 (1060)*
PVR ($dyn.s.cm^{-5}$)	1075 (576)	1027 (514)*	968 (483)*	880 (425)*

* $p < 0.05$ (compared with control values).

CI, cardiac index; HR, heart rate; LAP, left atrial pressure; MAP, mean systemic arterial pressure; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVR, systemic vascular resistance.

Table 2 Effects of epoprostenol (PGI_2) infusion on haemodynamic indices in 20 infants (mean (SD))

Index	Control (n = 20)	Dose of PGI_2		
		5 ng/kg/min (n = 20)	10 ng/kg/min (n = 20)	25 ng/kg/min (n = 15)
HR (beats/min)	156 (18)	162 (17)*	162 (16)*	168 (18)*
MAP (mm Hg)	54.4 (8.0)	54.2 (10.7)	50.2 (10.6)*	46.7 (9.4)*
PAP (mm Hg)	21.4 (4.9)	21.3 (5.2)	20.1 (4.6)*	19.7 (4.4)*
LAP (mm Hg)	8.0 (2.0)	8.4 (2.1)	8.4 (2.4)	8.3 (2.5)
RAP (mm Hg)	6.2 (2.1)	6.4 (2.3)	6.7 (2.2)*	6.9 (1.9)*
CI ($l/min/m^2$)	4.2 (1.3)	4.4 (1.3)*	4.6 (1.3)*	5.3 (1.6)*
SVR ($dyn.s.cm^{-5}$)	3875 (1227)	3584 (1176)*	3084 (982)*	2438 (757)*
PVR ($dyn.s.cm^{-5}$)	1100 (551)	996 (479)*	857 (382)*	702 (276)*

* $p < 0.05$ (compared with control values). See footnote to table 1 for abbreviations.

Figure 1 Effects of prostaglandin E₁ (PGE₁) and epoprostenol (PGI₂) on pulmonary vascular resistance (PVR). **p* < 0.05, for change from control values.

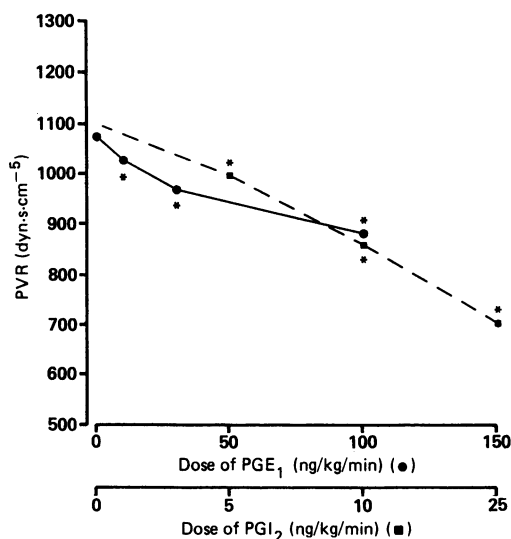


Figure 2 Effects of prostaglandin E₁ (PGE₁) and epoprostenol (PGI₂) on systemic vascular resistance (SVR). **p* < 0.05, for change from control values.

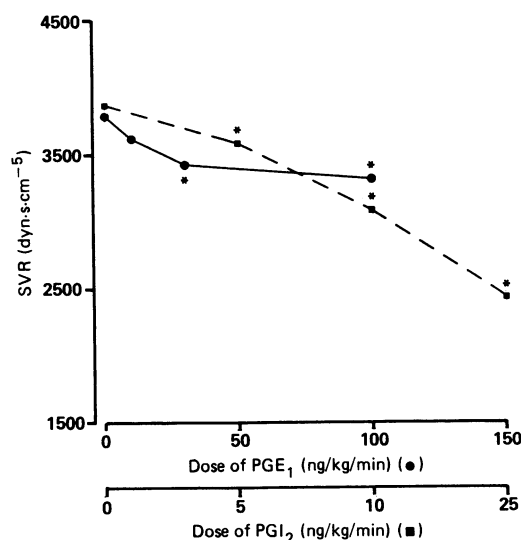
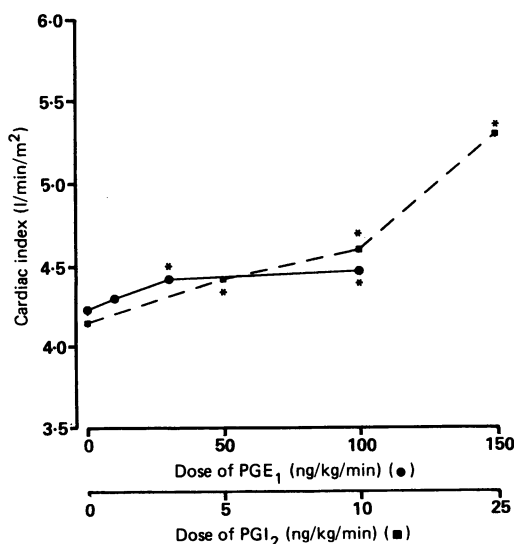


Figure 3 Effects of prostaglandin E₁ (PGE₁) and epoprostenol (PGI₂) on cardiac index. **p* < 0.05, for change from control values.



test; they did not reach statistical significance—that is, no difference was shown between the pulmonary specificity of the two drugs.

Discussion

We confirmed that both PGE₁ and epoprostenol are effective vasodilators, producing a decrease in systemic and pulmonary vascular resistances, but with no pulmonary specificity. Epoprostenol was 6–10 times more potent than PGE₁.

Haemodynamic function can change considerably as the circulation recovers from cardiopulmonary bypass. To minimise the effects of this we used each patient as his own control, randomised the order of the drugs, and limited each infusion period to 20 minutes. In our unit inotropic treatment (dopamine 5–10 µg/kg/min) and phenoxybenzamine are given routinely to infants after cardiopulmonary bypass. Dopamine at these doses may increase cardiac index and systemic pressure but does not significantly alter pulmonary artery pressure or the pulmonary vascular resistance.^{19,20} Phenoxybenzamine, a direct α adrenergic blocking agent,²¹ vasodilates all vascular beds; it is not known how this affects the actions of PGE₁ and epoprostenol and therefore our results may not be valid for patients who are not taking α adrenergic blocking agents.

Cardiac output measured by pulsed Doppler ultrasound accords closely with the results obtained by the Fick and dye dilution techniques in infants^{18,22}; the technique is simple, non-invasive, can be performed repeatedly, and is used in our unit as the standard measure of cardiac output. None of the potential sources of error such as aortic valve abnormalities, subcutaneous emphysema, or a significant intracardiac shunt were present in the patients we studied.

Rubis *et al* compared the effects of PGE₁ in children after open-heart surgery with those of sodium nitroprusside.⁷ Although both PGE₁ and sodium nitroprusside were effective vasodilators, PGE₁ produced a more variable response: high doses of PGE₁ (200–1000 ng/kg/min) produced troublesome side effects in five of their 26 patients, four of whom had an increase in pulmonary and systemic pressures. We used lower doses of PGE₁ in a younger, more homogeneous population, and all patients were sedated, ventilated, and receiving inotropic treatment. These factors probably explain the lack of adverse effects and the consistent vasodilatation we observed. The effects of epoprostenol in our patients accord with those reported in older children and adults: Bush *et al* studied the effects of epoprostenol in 20 children aged 2 months to 19 years with pulmonary hypertension caused by congenital heart disease, and showed a dose-dependent but non-selective vasodilatation.²³ In their study systemic hypotension occurred at doses higher than 20 ng/kg/min.

PGE₁ and epoprostenol were equally effective in infants with pulmonary hypertension after cardiac surgery. Because epoprostenol is more

expensive, we believe that PGE₁ is the preferred drug. As more is learned about the specific roles of the prostaglandins in the pathophysiology of pulmonary vascular disease, however, epoprostenol may become the drug of choice.

We thank Dr Peter Heery of Wellcome (Australia) for the supply of epoprostenol. JK is supported by a National Health and Medical Research Council Medical Postgraduate Research Fellowship.

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